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Organocatalyzed Tsuji–Trost reaction: a new method for the closure of five- and six-membered rings

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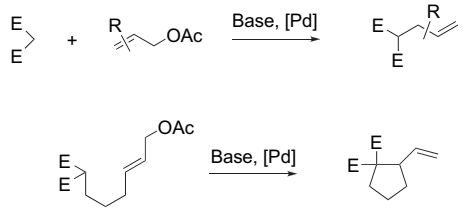
ABSTRACT

A combination of organotransition metal catalysis and organocatalysis allows for Tsuji–Trost 5-*exo*- and 6-*exo*-cyclizations of aldehydes. This transformation can also be accomplished as a catalytic asymmetric reaction, which affords vinylcyclopentane derivatives with up to 98%ee.

1. Introduction

Allylation of soft carbon nucleophiles with π-allylpalladium species is historically the first example of a Pd complex mediated carbon–carbon bond formation[1] and a highly useful synthetic transformation; this is also one of the first organotransition metal catalyzed named reactions, known as the Tsuji–Trost reaction.[2] The scope of the reaction is large and encompasses intermolecular bond forming reactions, as well as cyclizations (Scheme 1).[3] Initially stoichiometric, with respect to Pd species, the reaction was subsequently rendered catalytic,[4] which enabled the development of catalytic asymmetric variants.[5,6] However, an important limitation of the reaction scope was the necessity to use highly (i.e. doubly) stabilized enolates (such as malonates, β-keto esters, β-keto sulfoxides, etc.), while more attractive proenolates (ketones, esters, aldehydes) were not suitable reaction partners. The efforts invested to overcome this restriction met with some success at the intermolecular level,[7] where the proposed solutions relied on the combination of allylpalladium with preformed enolate chemistry,[8] including also the use of novel ligands, iridium-based catalysts,[9] additives,[10] or in situ formation of 'discrete enolate' species via the rearrangements of the corresponding allyl enol carbonates,[11] or allyl β-keto esters.[12] Aldehydes were allylated directly with allylic alcohols (via in situ formed enolates) under the modified conditions of the Tsuji–Trost reaction.[13] Surprisingly, no attempts have been made to surpass the aforementioned limitation when cyclizations are concerned: to the best of our knowledge, a single exception is the cyclization of a nitro derivative.[14] This example is specific, as the nitro group is the strongest electron-withdrawing group in organic chemistry, and the acidity of the α-hydrogen (pK_a=9) compares favorably with those in doubly activated proenolates (e.g. pK_a=11–13 for malonates, or β-keto esters).[15] In addition, examples of intramolecular allylation of 'ordinary' enolates are scarce and the reaction can be surprisingly difficult. In the literature we have found only four examples of intramolecular allylations of ester,[16] ketone[17] or amide enolates.[18] Recently, in a preliminary communication we reported a modification of the



Scheme 1. Inter- and intramolecular Tsuji–Trost reaction.

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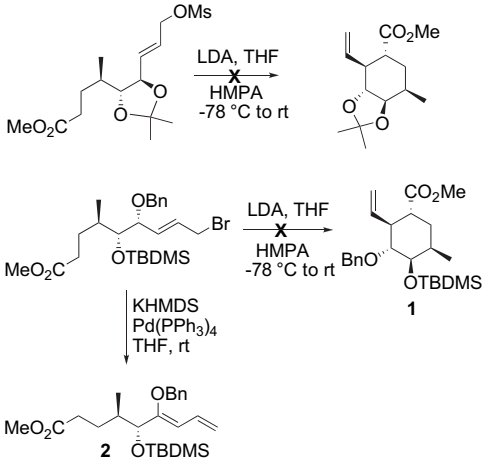
Tsuji–Trost reaction which allows for the intramolecular allylation of aldehydes.[19] We now wish to report a full account of this research.

2. Results and discussion

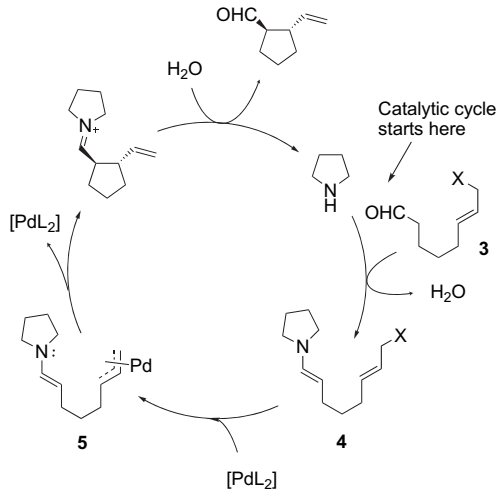
We faced the problem of intramolecular allylation in the course of a total synthesis of the antibiotic abyssomicin C: in the retrosynthetic analysis of this compound we relied on intramolecular allylation as a key step in the construction of the vinylcyclohexane core.[20] Unfortunately, the envisioned transformation was unfeasible: as delineated in Scheme 2, no reaction took place under conventional experimental conditions, while more energetic ones



Scheme 2. Attempted intramolecular allylation of esters.

brought about the rapid decomposition of substrates. In order to enhance the electrophilicity of the allylic part of the molecule, we attempted the enolate alkylation in the presence of catalytic $Pd(PPh_3)_4$, as the intramolecular Tsuji–Trost reaction. A very clean reaction gave a single compound in 87% yield; however, it turned out not to be the cyclization (**1**), but the elimination product **2**. Apparently, the ester enolate behaved more as a base, than as a nucleophile, promoting the elimination of HBr from the π-allylpalladium complex.[21]

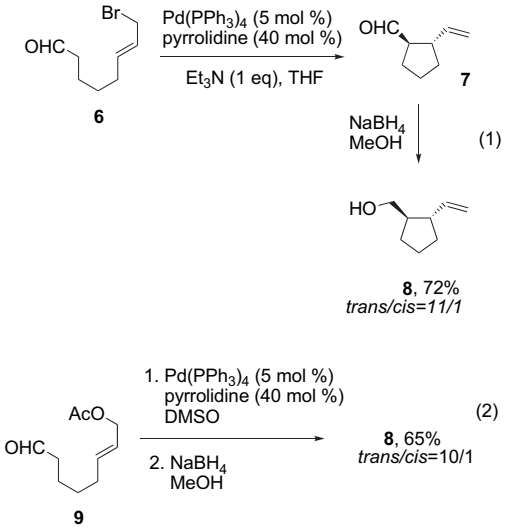
In the search for a softer nucleophile, we turned our attention toward enamines, whose use in intermolecular reactions with π-allylpalladium compounds has literature precedents.[1,22] Rather than preparing these intermediates in a separate synthetic step (which would be inconvenient for carbonyl compounds possessing an allylic halide functionality, and generally of limited synthetic value), we envisioned their formation in situ, within a catalytic cycle represented in Scheme 3. A salient feature of this concept is the combination of organotransition metal catalysis and organocatalysis[23]—an approach that, at the beginning of this research, to the best of our knowledge, has had a single precedent in the literature.[24] Thus, in the presence of a catalytic amount of a secondary amine, the aldehyde **3** should be in equilibrium with the corresponding enamine **4**. Simultaneously, Pd(0) species should form the π-allylpalladium complex at the allylic end of the molecule. These two concurrent processes should result in transient creation of two reacting centers in the same molecule (**5**) and, consequently, the formation of the carbon–carbon bond. However, the fact that both catalysts must operate in the same molecule was also the issue of some concern: given the reversible nature of all steps and the substoichiometric quantities of catalysts, it is not evident that the active intermediate **5**—enamine of the π-allylpalladium complex—would be present in sufficiently high concentration to secure an efficient



Scheme 3. Mechanism of the [Pd]/amine cocatalyzed cyclization.

synthetic transformation. Thus, the feasibility of the envisaged protocol had to be tested experimentally.

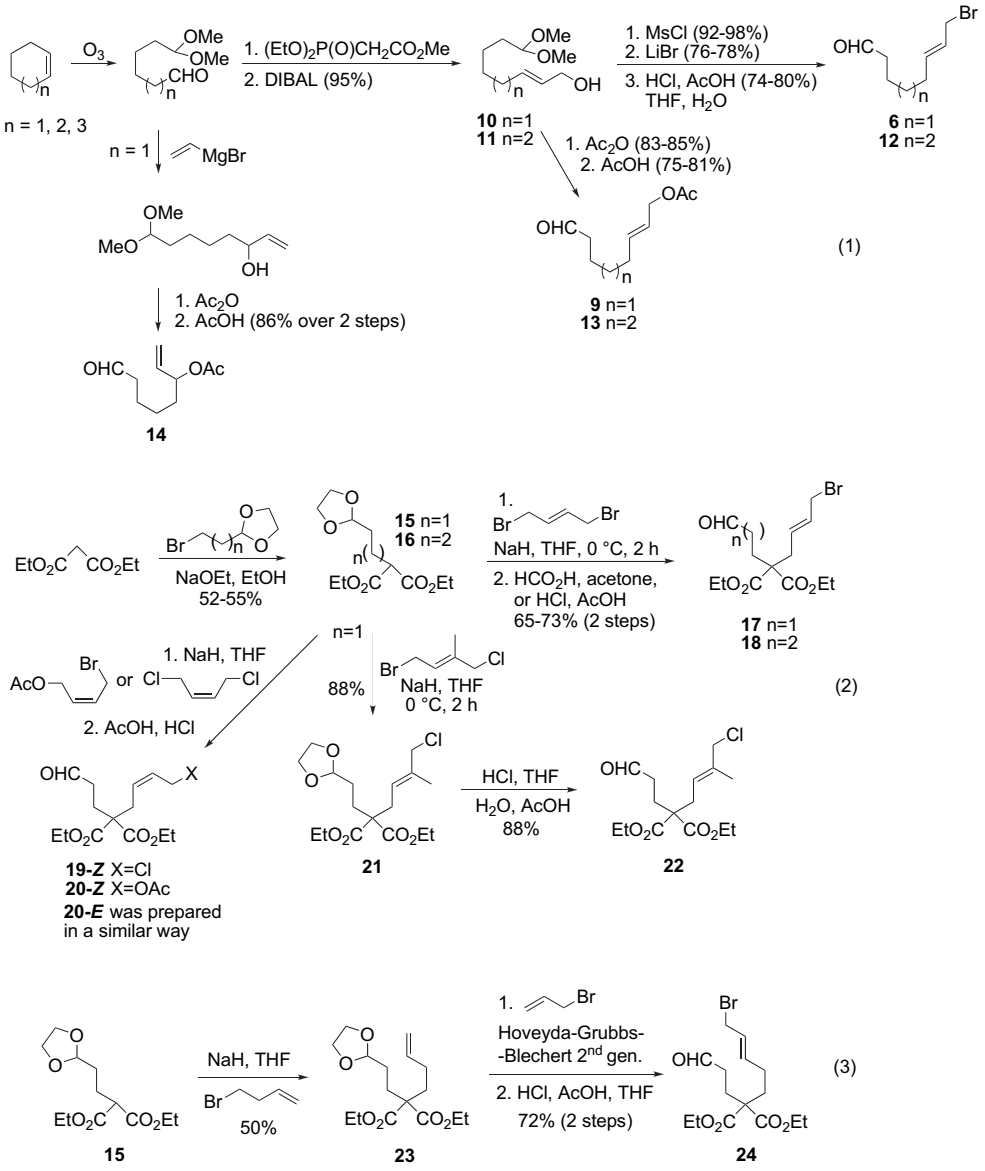
In the first experiment, bromoaldehyde **6** was treated with catalytic amounts of $Pd(PPh_3)_4$, pyrrolidine and one equivalent of triethylamine, in THF as solvent, at rt. To our delight, a rapid reaction gave rise to 2-vinyl-cyclopentanecarbaldehyde **7** which was isolated (as the corresponding alcohol **8**, after in situ reduction with $NaBH_4$, in order to avoid difficulties in the isolation of the volatile aldehyde) in 72% yield (Scheme 4, example 1). The cyclization was stereoselective, with the ratio of diastereoisomers *trans:cis*=11:1, as determined by ^1H NOESY NMR experiment.[25] No reaction took



Scheme 4. The first cyclization experiments.

place in the absence of any of the two catalysts, thus confirming the proposed mechanism. While this research was underway, Cordova reported a similar approach to the intermolecular allylation of carbonyl compounds, using allyl acetate as the electrophile, in DMSO as a solvent;[26] under these conditions aldehyde **9** cyclized with comparable yield and stereoselectivity (Scheme 4, example 2).

Encouraged by these preliminary results, we decided to study the scope and limitations of the reaction in more detail. For that purpose, a number of cyclization precursors were prepared, as represented in Scheme 5. Thus, ozonolysis of cycloalkenes, followed by the introduction of allylic alcohol functionalities by



Scheme 5. Preparation of precursors for carbocyclizations.

a standard HWE olefination/DIBAL reduction method, furnished compounds **10** and **11**, which were easily converted into cyclization precursors **6**, **9**, **12** and **13** (Scheme 5, path 1). Regioisomeric precursor **14** was also prepared, from the same starting compound. Alternatively, substrates for 5-*exo*- and 6-*exo*-carbocyclizations could be assembled by a malonate alkylation (Scheme 5, path 2). A reactive allylic halide structural unit could also be carried through synthetic steps in a latent form of a terminal alkene, and 'activated' in the penultimate step by cross-metathesis (Scheme 5, path 3).[27]

When submitted to the conditions for cyclizations, all precursors afforded vinylcyclopentane and vinylcyclohexane derivatives in good yields, thus confirming the generality of the procedure. The results of these experiments are summarized in Table 1. Thus, precursor **14**, regioisomeric to **6** and **9**, gave the same product **7**, albeit in somewhat lower yield and with much lower stereoselectivity (entry 3). Cyclization of malonate derivative **17** was complete within minutes (entry 4), indicating a strong, positive Thorpe-Ingold effect to the reaction rate and efficiency. The geometry of the allylic alkene proved to be without major influence to the reaction rate and stereoselectivity (compare entries 4 and 5). Surprisingly, acetates **20-*E*** and **20-*Z*** were inferior substrates, with respect to their halide analogues (entry 6). We were pleased to note that cyclizations with the introduction of isopropenyl group are also possible, given the frequent presence of this structural unit in natural products (entry 7). Unfortunately, cyclization of α-benzyloxy aldehyde **25** was less efficient and stereorandom (entry 8). The method proved suitable for the construction of cyclohexane derivatives, as both the acetate and halide precursors underwent smooth 6-*exo*-cyclizations (entries 9–12). However, 3-*exo*- and 7-*exo*-cyclizations did not occur under these conditions (entries 13–14).

With this new cyclization method in hand, we revisited our synthetic problem. Gratifyingly, the cyclization of **32** was complete within minutes at rt, affording the desired product **33** in 95% yield (entry 15). Oxidation of this intermediate with oxone gave the corresponding ester;[28] thus, the overall cyclization/oxidation sequence was a successful synthetic equivalent of the unfeasible ester enolate cyclization.

We next tested the applicability of the method to the formation of heterocycles. Precursors for the heterocyclization attempts were prepared by N-alkylation of sulfonamide anions, as shown in

Table 1
[Pd]/pyrrolidone cocatalysed 5-exo- and 6-exo- carbocyclizations of aldehydes

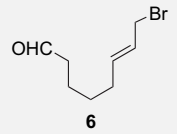
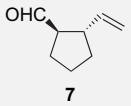
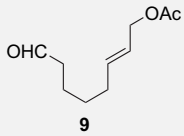
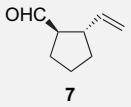
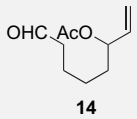
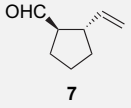
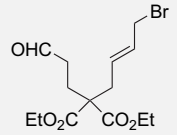
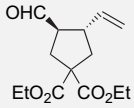
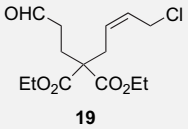
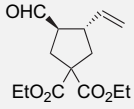
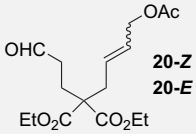
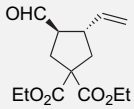
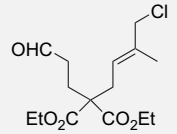
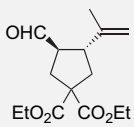
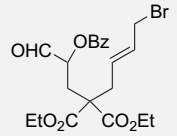
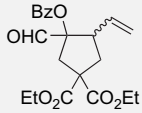
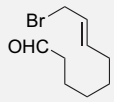
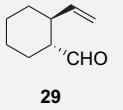
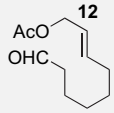
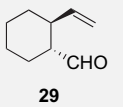
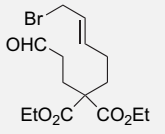
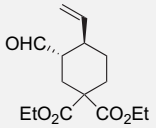
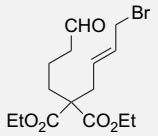
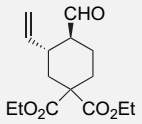
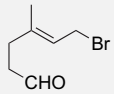
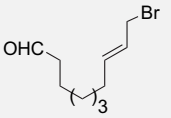
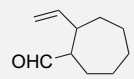
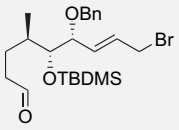
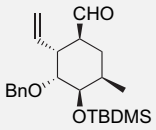
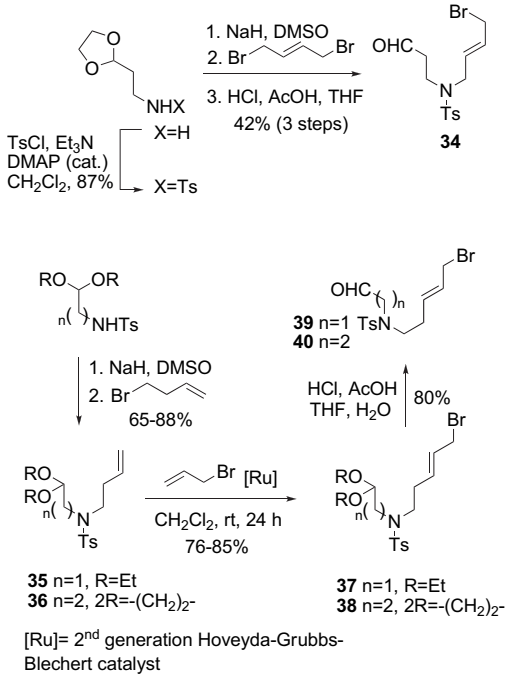
Entry	Reactant	Method[a]	Product	Yield[b] *trans*/*cis*
1	 **6**	A	 **7**	72%[c] 11/1
2	 **9**	B	 **7**	63%[c] 10/1
3	 **14**	B	 **7**	53% 2/1
4	 **17**	A	 **26**	75% 13/1
5	 **19**	A	 **26**	88% 7/1
6	 **20-*Z*** **20-*E***	B B	 **26**	14% 25%
7	 **22**	A	 **27**	67% 8/1
8	 **25**	A	 **28**	36% 1/1
9	 **12**	A	 **29**	60% 7/1
10	 **13**	B	 **29**	65% 10/1
11	 **24**	A	 **30**	88% 10/1

Table 1 (*continued*)

Entry	Reactant	Method[a]	Product	Yield[b] *trans*/*cis*
12	 **18**	A	 **31**	52% 12/1
13		A		0%
14		A		0%
15	 **32**	A	 **33**	95%[d] 7/1

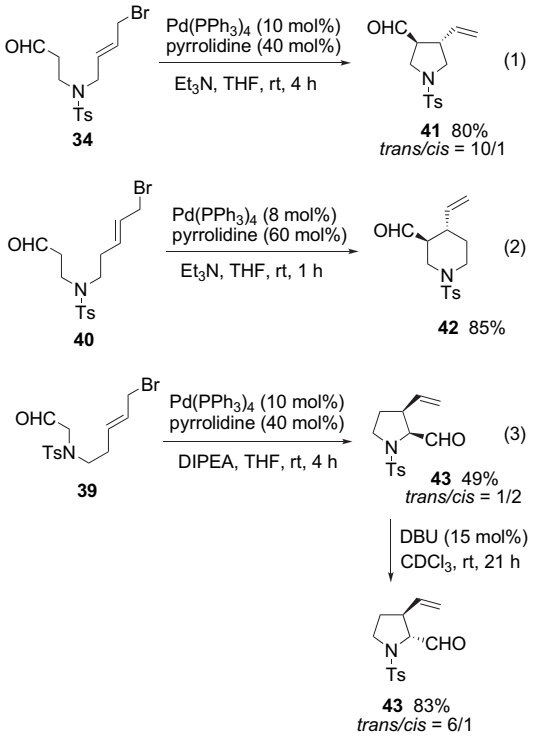
[a] Method A: $Pd(PPh_3)_4$ (5 mol %), Pyrrolidine (40 mol %), Et_3N (1 equiv), THF, rt, 30 min; Method B: $Pd(PPh_3)_4$ (5 mol %), Pyrrolidine (40 mol %), DMSO, rt, 30 min.
[b] Yields of isolated, pure compounds.
[c] Isolated as the corresponding alcohol, after the reduction with $NaBH_4$.
[d] 10 mol % of $Pd(PPh_3)_4$.

Scheme 6. Here again, cross metathesis was a useful way for the introduction of the activated allylic moiety.



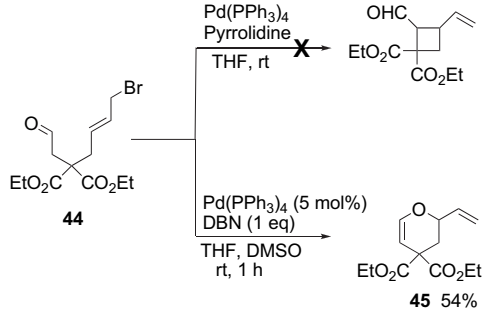
Scheme 6. Preparation of precursors for heterocyclizations.

The results of heterocyclization experiments are shown in Scheme 7. Gratifyingly, formation of both pyrrolidine and piperidine derivatives proceeded cleanly and in good yields. However, while the cyclizations shown in examples 1 and 2 proceeded with *trans*-selectivity, the cyclization of amidoaldehyde **39** afforded predominantly *cis*-configured vinylpyrrolidine **43**. Upon treatment with DBU, this compound could be isomerized into thermodynamically more stable *trans*-isomer of **43**.



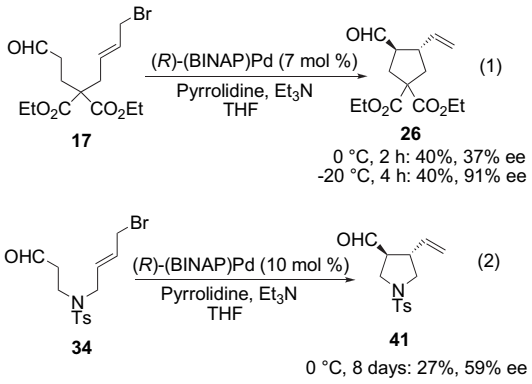
Scheme 7. Heterocyclizations.

One more example of heterocycle formation is worthy of mention: when submitted to standard reaction conditions, aldehyde **44**[29] did not undergo 4-*exo*-carbocyclization, but instead 6-*exo*-cyclization of the corresponding enole, to give dihydropyrane **45**. Substituting DBN for pyrrolidine improved the yield (Scheme 8). Although cyclizations of strongly activated enols (i.e. of β-dicarbonyl compounds, or β-keto esters) mediated by π-allylpalladium complexes are known in the literature,[30] to the best of our knowledge analogous heterocyclizations of simple aldehydes have not been reported so far.



Scheme 8. Dihydropyrane formation.

The next logical step was to examine whether the cyclization could be performed as a catalytic asymmetric reaction. Initial screening of organocatalysts[31] was not successful, as they either did not catalyze the reaction (MacMillan's catalyst, (*S*)-proline, (*S*)-2-diphenylprolinol), or failed to effect the asymmetric induction ((*S*)-2-methoxymethyl pyrrolidine). Better results were obtained when the role of the asymmetric inductor was conferred to the metal complex. Thus, reaction of **17** with 7 mol % of Pd[(*R*)-(+)-(BINAP)] catalyst at 0 °C afforded the product **26** with 37% ee, albeit in lower yield. However, lowering the temperature to −20 °C gave, after 4 h, the product **26** with 91% ee (Scheme 9, example 1). Similarly, optically enriched pyrrolidine derivative **41** was obtained with 59% ee, when the reaction was performed at 0 °C (example 2). However, in this case

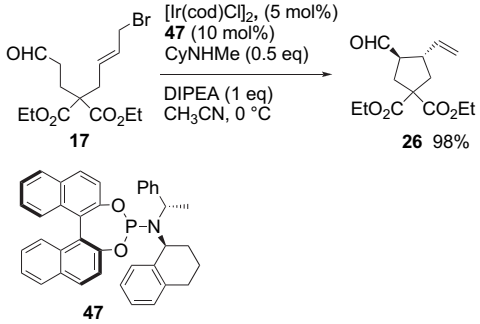


Scheme 9. Catalytic asymmetric cyclizations.

the reaction required 8 days for completion and, for practical reasons, it was not possible to run the cyclization at lower temperature.

Further optimization of the reaction, with respect to stereoselectivity, was performed with compounds of type **17**, **19**-***E***, **20**-***Z*** and **46**, and included variations of the solvent,[32] leaving group,[33] secondary amine catalyst[34] and a chiral ligand.[35] Selected results of this study are represented in Table 2. The highest level of asymmetric induction—>98%ee (entry 8)—was obtained when the reaction was performed in THF as a solvent, with phosphate leaving group, Ph–MeOBIPHEP as a chiral ligand and methyl cyclohexylamine as organocatalyst; in the case the reaction proceeded in good yield (76%) and satisfactory diastereoselectivity (*trans:cis*=7.4:1).[36]

Recently, highly enantioselective iridium-catalyzed allylation of enamines has been reported.[22b] Application of these reaction conditions to our system did not bring about significant levels of asymmetric induction. In order to enhance the enantioselectivity, a more voluminous ligand **47** was prepared. Surprisingly, under these modified reaction conditions, the levels of enantio- and diastereoselectivity were still low, but the ring closure occurred in almost quantitative yield (Scheme 10).



Scheme 10. Iridium-mediated cyclization.

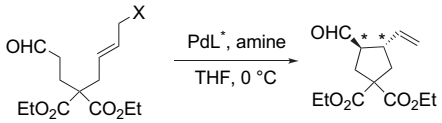
To summarize, organocatalyzed Tsuji–Trost reaction allows for the efficient cyclization of aldehydes containing a suitably positioned allylic moiety. Carbo- and heterocyclic, five- and six-membered rings were obtained in good yields and with reasonable diastereoselectivity. In the presence of chiral phosphine ligands, a catalytic asymmetric cyclization afforded vinylcyclopentane derivative with high levels of asymmetric induction. Research oriented toward the application of this reaction to natural products synthesis is underway.

3. Experimental

3.1. General experimental

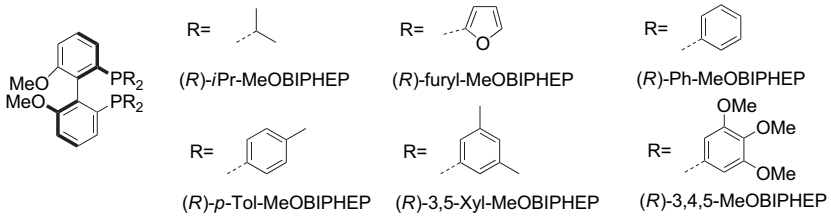
All chromatographic separations[37] were performed on Silica, 10–18, 60A, ICN Biomedicals. Standard techniques were used for

Table 2
Optimization of the catalytic asymmetric cyclization



26

Entry	Precursor	X	L	Amine	Yield	Optical purity	*trans*/*cis*
1	**20-*Z***	OAc	(*R*)-BINAP	Pyrrolidine	47%	52% ee	8/1
2	**17**	Br	(*R*)-BINAP	MeNHCy	36%	90% ee	5/1
3	**19-*E***	Cl	(*R*)-BINAP	Pyrrolidine	55%	82% ee	4.2/1
4	**19-*E***	Cl	(*R*)-BINAP	MeNHCy	67%	80% ee	14/1
5	**46**	$OP(O)(OEt)_2$	(*R*)-BINAP	Pyrrolidine	33%	94% ee	12/1
6	**46**	$OP(O)(OEt)_2$	(*R*)-*i*Pr-MeOBIPHEP	MeNHCy	56%	64% ee	7.1/1
7	**46**	$OP(O)(OEt)_2$	(*R*)-Furyl-MeOBIPHEP	MeNHCy	35%	92% ee	5.4/1
8	***46***	***$OP(O)(OEt)_2$***	***(R)-Ph-MeOBIPHEP***	***MeNHCy***	***76%***	***98% ee***	***7.4/1***
9	**46**	$OP(O)(OEt)_2$	(*R*)-*p*-Tol-MeOBIPHEP	MeNHCy	60%	98% ee	7.6/1
10	**46**	$OP(O)(OEt)_2$	(*R*)-3,5-Xyl-MeOBIPHEP	MeNHCy	71%	91% ee	8.5/1
11	**46**	$OP(O)(OEt)_2$	(*R*)-3,4,5-MeOBIPHEP	MeNHCy	67%	62% ee	9/1



the purification of reagents and solvents.[38] NMR spectra were recorded on a Varian Gemini 200 (^{1}H NMR at 200 MHz, ^{13}C NMR at 50 MHz, for samples in deuterated chloroform), and on Bruker Avance III 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz); chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard, coupling constants (J) are in Hertz. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200). Gas chromatography analyses were performed on a GC equipped with Split/Splitless injector (split 1:99), operated at 244 °C; Column: J&W Scientific HP-Chiral 20, 30 m, 0.25 mm i.d., 0.25 μm film; Carrier gas hydrogen, 1 mL/min measured at 210 °C. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Experimental procedures and spectral data for compounds **6**–**15**, **17**, **26**, **29**, **33**, **34** and **41** were provided in the preliminary communication.[39] Compound **44** was prepared as previously described.[29] Preparation of compounds **18**, **19**, **20-*E***, **20-*Z***, **25**, **28**, **31**, **45**, **46** and **47**, as well as cyclizations performed with Ir-catalyst, are described in Supplementary data.

3.2. Synthesis of precursors and cyclizations

*3.2.1. (E)-Diethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)-2-(4-chloro-3-methylbut-2-enyl)malonate (**21**).* Sodium hydride (43.7 mg; 1.82 mmol) was added to a cold (0 °C) solution of diethyl 2-(1,3-dioxolan-2-yl)-ethylmalonate[29] (389.5 mg; 1.50 mmol) in dry THF (4.5 mL). After 15 min of stirring, (*E*)-4-bromo-1-chloro-2-methylbut-2-ene[39] (682.7 mg; 3.78 mmol) was added, the reaction mixture was stirred for 30 min at 0 °C, followed by 1.5 h at rt, then diluted with dichloromethane (30 mL), washed with water, satd aq $NaHCO_3$, dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; eluent: petroleum–ether/EtOAc=9/1) afforded 478.4 mg (88%) of the title compound **21** as a colorless oil. TLC R_f 0.43 (petroleum–ether/EtOAc=3/1). IR_{film}: 2982, 2937, 2726, 1724, 1445, 1368, 1262, 1220, 1185, 1095, 1027, 684. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.42 (t, J=7.0 Hz, 1H), 4.86 (t, J=4.2 Hz, 1H), 4.18 (q, J=7.1 Hz, 4H), 4.00–3.80 (m, 6H), 2.64 (d, J=7.2 Hz, 2H), 2.04–1.96 (m, 2H), 1.75 (s, 3H), 1.63–1.52 (s, 2H), 1.24 (t, J=7.3 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.0 (C), 135.2 (C), 124.0 (CH), 103.9 (CH), 64.8 (CH_2), 61.2 (CH_2), 56.8 (C), 51.8 (CH_2), 31.2 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 14.3 (CH_3), 14.0 (CH_3). HRMS (ESI) calcd for: $C_{17}H_{28}ClO_6$ $[M+H]^+$: 363.1569, found: 363.1555; calcd for $C_{17}H_{27}ClO_6Na^+$ $[M+Na]^+$: 385.1388, found: 385.1374.

*3.2.2. (E)-Diethyl 2-(4-chloro-3-methylbut-2-enyl)-2-(3-oxopropyl)-malonate **22**.* Water (1.4 mL), acetic acid (1.4 mL) and 1:1 HCl (1.9 mL) were added to a solution of (*E*)-diethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)-2-(4-chloro-3-methylbut-2-enyl)malonate **21** (65.9 mg; 0.182 mmol) in THF (1.4 mL) and the resulting solution was stirred for 6 h at rt. The reaction was quenched by the addition of saturated aq $NaHCO_3$ (35 mL), extracted with ethyl acetate, dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=4/1) afforded 50.8 mg (88%) of the title compound **22** as a colorless oil. The compound is unstable, therefore it was used immediately in the next (cyclization) step. TLC R_f 0.31 (petroleum–ether/EtOAc=4/1). IR_{film}: 2980, 2884, 1726, 1446, 1264, 1218, 1184, 1143, 1095, 1027, 683. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.74 (s, 1H), 5.42 (t, J=7.0 Hz, 1H), 4.19 (q, J=7.0 Hz, 4H), 3.98 (s, 2H), 2.65 (d, J=7.4 Hz, 2H), 2.52–2.45 (m, 2H), 2.22–2.15 (m, 2H), 1.76 (s, 3H), 1.26 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 200.7 (CH), 170.8 (C), 135.7 (C), 123.6 (CH), 61.5 (CH_2), 56.4 (C), 51.7 (CH_2), 39.2 (CH_2), 32.1 (CH_2), 25.1 (CH_2), 14.4 (CH_3), 14.0 (CH_3). HRMS (ESI) calcd for $C_{15}H_{23}ClO_5Na^+$ $[M+Na]^+$: 341.1126, found: 341.1123.

*3.2.3. 5-Exo-carbocyclization: trans-diethyl 3-formyl-4-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate **27**.* $Pd(PPh_3)_4$ (1.6 mg; 1.4 μmol) was added to a solution of **22** (6.6 mg; 21 μmol) in THF (0.1 mL), followed by the addition of pyrrolidine (4.5 μL; 54 μmol) and

triethylamine (3.1 μL; 22 μmol) and the resulting solution was stirred at rt under an argon atmosphere. After 2 h silica (33 mg) was added, and the resulting mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=7/1) afforded 3.9 mg (67%) of the title compound **27**, as a colorless oil. The compound was obtained as a mixture of diastereoisomers in a ratio *trans*:*cis*=8:1, as determined by GC. TLC R_f 0.53 (petroleum–ether/EtOAc=3/1). IR_{film}: 2981, 1726, 1445, 1368, 1252, 1179, 1096, 896. ^1H NMR (for **27**-*trans*; 200 MHz, $CDCl_3$) δ: 9.58 (d, J=2.4 Hz, 1H), 4.84 (s, 2H), 4.20 (q, J=7.1 Hz, 4H), 2.98–2.76 (m, 2H), 2.63–2.49 (m, 3H), 2.20–2.08 (m, 1H), 1.75 (s, 3H), 1.26 (t, J=7.1 Hz, 6H). ^{13}C NMR (for **27**-*trans*; 50 MHz, $CDCl_3$) δ: 201.9 (CH), 171.7 (C), 143.7 (C), 112.1 (CH_2), 61.8 (CH_2), 59.0 (C), 54.2 (CH), 47.6 (CH), 39.0 (CH_2), 33.9 (CH_2), 20.2 (CH_3), 13.9 (CH_3). HRMS (ESI) calcd for: $C_{15}H_{23}O_5^+$ $[M+H]^+$: 283.1540, found: 283.1540.

3.3. Synthesis of precursor 24 for 6-*exo*-carbocyclization

*3.3.1. (E)-Diethyl 2-but-3-enyl-2-(2-(1,3-dioxolan-2-yl)ethyl)malonate **23**.* Sodium hydride (62.5 mg; 2.60 mmol) was added to a cold (0 °C) solution of diethyl 2-(1,3-dioxolan-2-yl)-ethylmalonate **15** (520.5 mg; 2.00 mmol) in dry THF (6.6 mL), followed by the addition (after 15 min) of 4-bromobut-2-ene (0.31 mL; 3.05 mmol), and the resulting mixture was allowed to attain rt, with stirring overnight under an argon atmosphere. As the conversion was not complete, additional sodium hydride (22 mg; 0.92 mmol) and 4-bromobut-2-ene (0.11 mL; 1.08 mmol) were added, followed by stirring overnight and this procedure was repeated twice. The reaction was quenched by the addition of methanol (0.4 mL) and water (2 mL), extracted with dichloromethane, washed with aq $NaHCO_3$ and brine, dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; eluent: petroleum–ether/EtOAc=43/7) afforded 311.6 mg (50%) of the title compound **23** as a colorless oil. TLC R_f 0.53 (petroleum–ether/EtOAc=3/1). IR_{ATR}: 3078, 2979, 2883, 1725, 1641, 1450, 1261, 1186, 1141, 1026. ^1H NMR (200 MHz, $CDCl_3$): δ 5.85–5.70 (m, 1H), 5.07–4.94 (m, 2H), 4.87 (t, J=4.5 Hz, 1H), 4.18 (q, J=7.1 Hz, 4H), 4.01–3.81 (m, 4H), 2.07–1.96 (m, 6H), 1.62–1.52 (m, 2H), 1.25 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.4 (C), 137.5 (CH), 114.9 (CH_2), 104.0 (CH), 64.9 (CH_2), 61.1 (CH_2), 56.7 (C), 31.5 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 26.3 (CH_2), 14.0 (CH_3). HRMS (ESI) calcd for $C_{16}H_{27}O_6^+$ $[M+H]^+$: 315.1802, found: 315.1805; calcd for $C_{16}H_{26}O_6Na^+$ $[M+Na]^+$: 337.1622, found: 337.1624.

3.3.2. (E)-Diethyl 2-(5-bromopent-3-enyl)-2-(2-(1,3-dioxolan-2-yl-ethyl))malonate. A solution of (*E*)-diethyl 2-but-3-enyl-2-(2-(1,3-dioxolan-2-yl)ethyl)malonate **23** (104.2 mg; 0.331 mmol), allyl bromide (60 μL; 0.693 mmol) and second generation Grubbs–Hoveyda–Blechert catalyst (4 mg; 6 μmol) in dichloromethane (0.4 mL) was stirred 5 h under an argon atmosphere. Another portion of allyl bromide and the catalyst was added (same amounts as for the first addition), and stirring was continued overnight. Additional allyl bromide (60 μL; 0.693 mmol) and the catalyst (8.4 mg; 13 μmol) were added, and stirring was continued for six more hours. Silica (500 mg) was added, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=7/1) to afford 80.1 mg (59%) of the title compound as a yellow oil, accompanied by 37 mg of the starting compound (the yield calculated on the basis of the recovered starting compound was 92%). The reaction can also be performed at reflux, when the title compound was obtained in 86% yield. However, in this case the product is contaminated by a small amount of impurity which cannot be separated by column chromatography. IR_{ATR}: 2978, 2883, 1724, 1660, 1448, 1187, 1143, 1024. ^1H NMR (200 MHz, $CDCl_3$): δ 5.74–5.70 (m, 2H), 4.86 (t, J=4.6 Hz, 1H), 4.19 (q, J=7.1 Hz, 4H), 4.01–3.81 (m, 6H), 2.06–1.94 (m, 6H), 1.62–1.51 (m, 2H), 1.25 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.2 (C), 134.9 (CH), 126.9 (CH), 103.9 (CH), 64.9 (CH_2), 61.2 (CH_2), 56.6 (C), 33.0 (CH_2), 31.4 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 14.0 (CH_3). HRMS (ESI) calcd for $C_{17}H_{28}BrO_6^+$ $[M+H]^+$: 407.1064, found: 407.1063; calcd for $C_{17}H_{27}BrO_6Na^+$ $[M+Na]^+$: 429.0883, found: 429.0884; calcd for $C_{17}H_{27}BrO_6K^+$ $[M+K]^+$: 445.0623, found: 445.0628.

*3.3.3. (E)-Diethyl 2-(5-bromo-pent-3-enyl)-2-(3-oxo-propyl)malonate **24**.* Water (1.2 mL), acetic acid (1.2 mL) and 1:1 HCl (1.8 mL) were added to a solution of (*E*)-diethyl 2-(5-bromopent-3-enyl)-2-(2-(1,3-dioxolan-2-yl-ethyl))malonate (47 mg; 0.115 mmol) in THF (1.2 mL) and the resulting solution was stirred for 17 h at rt. The reaction was quenched by the addition of saturated aq $NaHCO_3$ (25 mL), extracted with ethyl acetate, dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=3/1) afforded 32.1 mg (77%) of the title compound **24** as a pale yellow oil. TLC R_f 0.40 (petroleum–ether/EtOAc=3/1). IR_{ATR}: 2980, 2725, 1724, 1447, 1251, 1189, 1096, 1026, 673. ^1H NMR (200 MHz, $CDCl_3$): δ 9.76 (bs, 1H), 5.79–5.56 (m, 2H), 4.20 (q, J=7.1 Hz, 4H) 4.02 (d, J=5.6 Hz, 2H), 2.52–2.44 (m, 2H), 2.24–2.16 (m, 2H), 2.00–1.98 (m, 4H), 1.26 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.6 (CH), 170.9 (C), 134.1 (CH), 126.8 (CH), 61.4 (CH_2), 56.3 (C), 44.9 (CH_2), 39.1 (CH_2), 32.4 (CH_2), 26.7 (CH_2), 24.9 (CH_2), 14.0 (CH_3). HRMS (ESI) calcd for $C_{15}H_{23}O_5^+$ $[M-Br]^+$: 283.1540, found: 283.1541.

*3.3.4. 6-Exo-carbocyclization: trans-diethyl 3-formyl-4-vinyl-cyclohexane-1,1-dicarboxylate **30**.* $Pd(PPh_3)_4$ (7.2 mg; 6 μmol) was added to a solution of **24** (28.2 mg; 78 μmol) in THF (0.9 mL) and the resulting solution was stirred under an argon atmosphere for 10 min, when pyrrolidine (2.6 μL; 31 μmol) and triethylamine (11.5 μL; 82 μmol) were added. After 1 h of stirring at rt TLC indicated the presence of 24; therefore, in order to achieve the full conversion of the starting material, the same amount of pyrrolidine was added two more times, in 30 min intervals. After 2 h (from the beginning) the reaction was complete, when silica was added (155 mg) and the resulting mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=100/8) afforded 19.2 mg (88%) of the title compound **30**, as a clear oil. The product was obtained as a mixture of diastereoisomers in a ratio *trans*:*cis*=10:1, as determined by the integration of the corresponding aldehyde peaks in ^1H NMR spectrum. TLC R_f 0.49 (petroleum–ether/EtOAc=4/1). IR_{ATR}: 2980, 2937, 2868, 1722, 1640, 1448, 1367, 1231, 1202, 1153, 1093, 1022, 921, 861. ^1H NMR (500 MHz, $CDCl_3$): δ 9.65 (d, J=2.5 Hz, 1H), 5.75–5.68 (m, 1H) 5.09–5.05 (m, 2H), 4.23 (d, J=7.2 Hz, 2H), 4.17 (d, J=7.2 Hz, 2H), 2.50–2.47 (m, 2H), 2.41–2.38 (m, 1H), 2.24–2.18 (m, 1H), 1.81–1.67 (m, 3H), 1.27 (t, J=7.2 Hz, 3H), 1.24 (t, J=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5 (CH), 171.6 (C), 170.4 (C), 139.8 (CH), 116.1 (CH_2), 61.6 (CH_2), 61.4 (CH_2), 53.7 (C), 50.2 (CH), 41.8 (CH), 30.0 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 14.0 (CH_3), 14.0 (CH_3). HRMS (ESI) calcd for: $C_{15}H_{23}O_5^+$ $[M+H]^+$: 283.1540, found: 283.1532; calcd for $C_{15}H_{22}O_5Na^+$ $[M+Na]^+$: 305.1359, found: 305.1357.

3.4. Synthesis of precursor 39 for 5-*exo*-heterocyclization

*3.4.1. N-(But-3-enyl)-N-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide **35**.* Dimsyl anion (5 mL of 0.22 M solution in DMSO) was added to a solution of *N*-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide[40] (300 mg; 1.044 mmol) and the reaction mixture was stirred for 30 min under an argon atmosphere. 4-Bromo-1-butene (150 μL; 1.48 mmol) was added to the reaction and the mixture was vigorously stirred for 2.5 h. The successive

additions of the same amounts of dimsyl anion and 4-bromo-1-butene were performed five more times, when TLC of the mixture indicated the full consumption of the starting sulfonamide. The reaction mixture was diluted with brine (100 mL), extracted with ether, dried over anh. $MgSO_4$, concentrated under reduced pressure and purified by dry-flash chromatography (SiO_2; eluent: petroleum–ether/EtOAc=7/1), to give 292 mg (82%) of the title compound **35** as a colorless oil which soldifies at −20 °C. TLC R_f 0.41 (petroleum–ether/EtOAc=7/1). IR_{film}: 3075, 2976, 2928, 1641, 1598, 1342, 1157, 1121, 1090, 1060. ^1H NMR (200 MHz, $CDCl_3$): δ 7.73–7.69 (m, 2H), 7.32–7.27 (m, 2H), 5.77–5.57 (m, 1H), 5.05–4.95 (m, 2H), 4.63 (t, J=5.5 Hz, 1H), 3.80–3.46 (m, 4H), 3.33–3.19 (m, 4H), 2.42 (s, 3H), 2.35–2.24 (m, 2H), 1.20 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.3 (C), 137.1 (C), 134.8 (CH), 129.6 (CH), 127.2 (CH), 116.8 (CH_2), 102.9 (CH), 63.6 (CH_2), 51.0 (CH_2), 49.3 (CH_2), 32.7 (CH_2), 21.4 (CH_3), 15.3 (CH_3). HRMS (ESI) calcd for $C_{17}H_{27}NO_4SNa^+$ $[M+Na]^+$: 364.1553, found: 364.1545; calcd for $C_{17}H_{27}NO_4SK^+$ $[M+K]^+$: 380.1292, found: 380.1284.

3.4.2. (E)-N-(5-Bromopent-3-enyl)-N-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide ***37***. A solution of *N*-(but-3-enyl)-*N*-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide **35** (94.1 mg; 275 μmol), allyl bromide (50 μL; 585 μmol) and Hoveyda–Grubbs–Blechert second generation catalyst (11.9 mg; 19 μmol) in dry dichloromethane (2.7 mL) was stirred at rt, under an argon atmosphere. After 12 h, additional amounts of allyl bromide (45 μL; 532 μmol) and the ruthenium catalyst (8.6 mg; 14 μmol) were added and the reaction mixture was stirred for 2 h. The crude reaction mixture was evaporated with SiO_2 (1 g) and purified by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=15/1), to give first 34.1 mg of the starting compound **35**, followed by 68.5 mg (57%; yield calculated on the basis of the recovered starting compound is 90%) of the title compound **37**, as a light-brown oil. The product **37** is obtained as a mixture of geometric isomers in a ratio: *E*/*Z*=8/1, as determined by integration of the corresponding doublets in ^1H NMR, at 3.93 and 3.87 ppm. TLC R_f 0.21 (petroleum–ether/EtOAc=9/1). IR_{film}: 2963, 2925, 2855, 1599, 1342, 1261, 1158, 1093, 1065, 1023, 804. ^1H NMR (200 MHz, $CDCl_3$): δ 7.74–7.68 (m, 2H), 7.33–7.29 (m, 2H), 5.75–5.51 (m, 2H), 4.62 (t, J=5.5 Hz, 1H) 3.87 (d, J=6.4 Hz, 2H), 3.79–3.45 (m, 4H), 3.32–3.18 (m, 4H), 2.43 (s, 3H), 2.38–2.28 (m, 2H), 1.20 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 143.4 (C), 137.0 (C), 132.1 (CH), 129.7 (CH), 128.6 (CH), 127.2 (CH), 102.8 (CH), 63.6 (CH_2), 51.1 (CH_2), 49.0 (CH_2), 32.7 (CH_2), 31.1 (CH_2), 21.4 (CH_3), 15.3 (CH_3). HRMS (ESI) calcd for $C_{18}H_{28}NO_4SBrNa^+$ $[M+Na]^+$: 456.0815, found: 456.0812.

3.4.3. (E)-N-(5-Bromopent-3-enyl)-4-methyl-N-(2-oxoethyl)benzenesulfonamide ***39***. A solution of (*E*)-*N*-(5-bromopent-3-enyl)-*N*-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide **37** (58.1 mg; 134 μmol), THF (0.96 mL), water (0.96 mL), acetic acid (0.96 mL) and 6 M hydrochloric acid (1.5 mL) was stirred at rt for 2.5 h. The reaction mixture was neutralized by the addition of saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc. The extract was dried over anh. $MgSO_4$, concentrated under reduced pressure and purified by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=2/1), to give 35.5 mg (74%) of the title compound **39** as a light-yellow oil. Due to its' high proclivity toward degradation on standing, this compound was immediately used in the cyclization reaction. TLC R_f 0.36 (petroleum–ether/EtOAc=2/1). IR_{film}: 2923, 2853, 1732, 1597, 1336, 1154, 969, 546. ^1H NMR for the (*E*)-isomer (200 MHz, $CDCl_3$): δ 9.61 (t, J=1.4 Hz, 1H), 7.72–7.68 (m, 2H), 7.36–7.31 (m, 2H), 5.75–5.54 (m, 2H), 4.00–3.97 (m, 2H), 3.84–3.83 (d, J=1.4 Hz, 2H), 3.26 (t, J=7.4 Hz, 2H), 2.44 (s, 3H), 2.35–2.26 (m, 2H). ^{13}C NMR for the (*E*)-isomer (50 MHz, $CDCl_3$): δ 198.3 (CH), 144.1 (C), 135.5 (C), 130.7 (CH), 129.9 (CH), 129.1 (CH), 127.3 (CH), 57.2 (CH_2), 48.9 (CH_2), 44.5 (CH_2), 31.2 (CH_2), 21.5 (CH_3). HRMS (ESI) calcd for $C_{14}H_{19}O_3SBrN^+$ $[M+H]^+$: 360.0263, found: 360.0246.

3.4.4. 5-Exo-heterocyclization of 39: cis-1-tosyl-3-vinylpyrrolidine-2-carbaldehyde ***43****-cis.* Pyrrolidine (19 μL of the 0.6 M solution in THF; 11 μmol) and DIPEA (9.5 μL; 54 μmol) were added to a solution of **39** (19.5 mg; 54 μmol) and $Pd(PPh_3)_4$ (4.3 mg; 4 μmol) in THF (0.9 mL), and the resulting solution was stirred at rt, under an argon atmosphere. After 1 h, additional pyrrolidine (5 μL of the 0.6 M solution in THF; 3 μmol) and DIPEA (1.5 μL; 8 μmol) were added. As the conversion of the starting compound was not complete, pyrrolidine (5 μL of the 0.6 M solution in THF; 3 μmol) was added every 30 min; the reaction was complete after a total of 55 mol % of pyrrolidine was added. Silica (80 mg) was added, the resulting mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2; eluent: petroleum–ether/EtOAc=2/1), to give 8.1 mg (54%) of compound **43** as a light-yellow oil. The product was obtained as a mixture of stereoisomers in a ratio: *cis*/*trans*=2.4/1, as determined from ^1H NMR spectrum. The relative stereochemistry of isomers was determined by NOESY (see the Supplementary data). TLC R_f 0.48 (petroleum–ether/EtOAc=2/1). IR_{film}: 2925, 1733, 1643, 1597, 1347, 1161, 1094, 665, 591, 549. ^1H NMR for 43-*cis* (500 MHz, $CDCl_3$): δ 9.59 (d, J=3.5 Hz, 1H), 7.72 (d, J=8.0 Hz, 2H), 7.35 (d, J=8.0 Hz, 2H), 5.79–5.72 (m, 1H), 5.17–5.12 (m, 2H), 3.90 (dd, J=8.5 Hz, J=3.5 Hz, 1H), 3.76–3.72 (dt, J=9.7 Hz, J=6.0 Hz, 1H), 3.26 (dt, J=9.7 Hz, J=7.7 Hz, 1H), 2.96–2.88 (m, 1H), 2.45 (s, 3H), 1.90 (dt, J=6.0 Hz, J=7.5 Hz, 2H). ^{13}C NMR for 43-*cis* (125 MHz, $CDCl_3$): δ 200.0 (CH), 144.1 (C), 133.7 (C), 133.0 (CH), 129.9 (CH), 127.7 (CH), 118.6 (CH_2), 68.8 (CH), 48.0 (CH_2), 47.0 (CH), 30.6 (CH_2), 21.6 (CH_3). HRMS (ESI) calcd for $C_{14}H_{17}NO_3S^+$ $[M]^+$: 279.0924, found: 279.0924; calcd for $C_{14}H_{18}NO_3S^+$ $[M+H]^+$: 280.1002, found: 280.0999; calcd for $C_{14}H_{17}NO_3SNa^+$ $[M+Na]^+$: 302.0821, found: 302.0808; calcd for $C_{14}H_{17}NO_3SK^+$ $[M+K]^+$: 318.0561, found: 315.0567.

3.4.5. ***43****-Trans (from* ***43****-cis, by a base-catalyzed isomerization).* DBU (0.4 μL, 2.5 μmol, 16 mol %) was added to a solution of **43**-*cis* (4.5 mg; 16 μmol) in deuterated chloroform (250 μL) and the reaction mixture was filled with argon (the reaction took place in an NMR tube). After 20 h ^1H NMR indicated the ratio of isomers *trans*/*cis*=6.1/1.0. The reaction mixture was diluted with dichloromethane, washed with aqueous HCl (2%), saturated aqueous $NaHCO_3$ and brine, dried over anh. $MgSO_4$, and the solvent was removed under reduced pressure, to give 3.7 mg (83%) of **43**-*trans* as a colorless oil (*trans* isomer predominating in a 6.1/1 ratio). TLC R_f 0.48 (petroleum–ether/EtOAc=2/1). ^1H NMR (500 MHz, $CDCl_3$): δ 9.62 (d, J=3.0 Hz, 1H), 7.72 (d, J=8.0 Hz, 2H), 7.35 (d, J=8.0 Hz, 2H), 5.46–5.39 (m, 1H), 5.00–5.97 (m, 2H), 3.58–3.54 (m, 1H), 3.53 (dd, J=7.5 Hz, J=3.0 Hz, 1H), 3.40–3.36 (m, 1H), 2.96–2.88 (m, 1H), 2.45 (s, 3H), 2.05–1.99 (m, 1H), 1.53–1.46 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.5 (CH), 144.2 (C), 135.0 (CH), 133.5 (C), 129.9 (CH), 127.7 (CH), 117.5 (CH_2), 71.0 (CH), 48.1 (CH_2), 44.6 (CH), 30.9 (CH_2), 21.5 (CH_3).

3.5. Synthesis of precursor 40 for 6-*exo*-heterocyclization

3.5.1. N-(2-(1,3-Dioxolan-2-yl)ethyl)-N-(but-3-enyl)-4-methylbenzenesulfonamide ***36***. Dimsyl anion (14.8 mL of the 0.223 M solution in DMSO; 3.31 mmol; 1.1 equiv) was added to a solution of *N*-(2-(1,3-dioxolan-2-yl)ethyl)-4-methylbenzenesulfonamide (800.1 mg; 2.95 mmol) in DMSO (14.8 mL), and the solution was stirred 30 min at rt, under an argon atmosphere. 4-Bromobut-1-ene (0.4 mL; 3.94 mmol; 1.3 equiv) was added and the reaction mixture was stirred for 30 min. As the conversion of the starting sulfonamide was not complete, additional dimsyl anion (4.1 mL; 0.92 mmol; 0.3 equiv) was

added, followed by 4-bromobut-1-ene (0.15 mL; 1.47 mmol; 0.5 equiv), followed by 10 min of stirring at rt, and this procedure had to be repeated six times in order to complete the reaction. The reaction mixture was carefully diluted with brine (150 mL), extracted with ether, dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification by dry-flash chromatography (SiO_2; petroleum–ether/EtOAc=4/1) afforded 823.1 mg (86%) of the title compound **36** as a viscous pale-yellow oil which solidifies at −20 °C. TLC R_f 0.31 (petroleum–ether/EtOAc=3/1). IR_{ATR}: 2883, 1641, 1597, 1337, 1156, 666, 546. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.70 (d, J=7.8 Hz, 2H), 7.29 (d, J=7.8 Hz, 2H), 5.83–5.62 (m, 1H), 5.11–5.00 (m, 2H), 4.85 (t, J=4.5 Hz, 1H), 3.97–3.77 (m, 4H), 3.31–3.15 (m, 4H), 2.41 (s, 3H), 2.35–2.25 (m, 2H), 1.96–1.86 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 143.0 (C), 136.5 (C), 134.4 (CH), 129.5 (CH), 126.9 (CH), 116.9 (CH_2), 101.9 (CH), 64.7 (CH_2), 47.6 (CH_2), 43.1 (CH_2), 32.8 (CH_2), 32.7 (CH_2), 21.2 (CH_3). HRMS (ESI) calcd for $C_{16}H_{24}NO_4S^+$ $[M+H]^+$: 326.1421, found: 326.1433; calcd for: $C_{16}H_{23}NO_4SNa^+$ $[M+Na]^+$: 348.1240, found: 348.1241.

*3.5.2. (E)-N-(2-(1,3-Dioxolan-2-yl)ethyl)-N-(5-bromopent-3-enyl)-4-methylbenzenesulfonamide **38**.* Starting from **36**, according to the procedure for (*E*)-*N*-(5-bromopent-3-enyl)-*N*-(2,2-diethoxyethyl)-4-methylbenzenesulfonamide **37**, 42% of **38** was obtained (76% calculated on the basis of the recovered starting compound **36**). When the reaction was performed at 40 °C, for 48 h, the isolated yield was 80%, but the product contained a small amount of impurity which was impossible to separate by column chromatography. TLC R_f 0.21 (petroleum–ether/EtOAc=3/1). IR_{ATR}: 2953, 2883, 1597, 1337, 1156, 549. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.69 (d, J=8.0 Hz, 2H), 7.30 (d, J=7.8 Hz, 2H), 5.82–5.58 (m, 2H), 4.85 (t, J=4.50 1H), 3.98–3.76 (m, 6H), 3.33–3.14 (m, 4H), 2.42 (s, 3H), 2.38–2.28 (m, 2H), 1.96–1.86 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 143.2 (C), 136.5 (C), 131.9 (CH), 129.6 (CH), 128.7 (CH), 127.1 (CH), 102.0 (CH), 64.8 (CH_2), 47.5 (CH_2), 43.2 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 31.3 (CH_2), 21.4 (CH_3). HRMS (ESI) calcd for $C_{17}H_{25}BrNO_4S^+$ $[M+H]^+$: 418.0682, found: 418.0670; calcd for $C_{17}H_{24}BrNO_4SNa^+$ $[M+Na]^+$: 440.0502, found: 440.0484.

*3.5.3. (E)-N-(5-Bromopent-3-enyl)-4-methyl-N-(3-oxopropyl)benzenesulfonamide **40**.* A solution of (*E*)-*N*-(2-(1,3-dioxolan-2-yl)ethyl)-*N*-(5-bromopent-3-enyl)-4-methylbenzenesulfamide **38** (57.5 mg; 0.137 mmol), THF (1.25 mL), water (1.0 mL), acetic acid (1.25 mL) and 6 M HCl (1.7 mL) was stirred under an argon atmosphere for 16 h. The reaction mixture was neutralized (pH 8) by the addition of saturated aq $NaHCO_3$ (30 mL), extracted with EtOAc, dried over anh. $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2; petroleum-ether/EtOAc=2/1) afforded 40.1 mg (78%) of the title compound **40** as a pale-yellow oil. The product was obtained as a mixture of geometrical isomers, in a ratio: *E*/*Z*=6/1, as determined by the integration of peaks at 4.05 and 3.99 ppm in the ^1H NMR spectrum. TLC R_f 0.31 (petroleum–ether/EtOAc=2/1). IR_{ATR}: 2927, 1721, 1597, 1335, 1155, 548. ^1H NMR (200 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 7.68 (d, J=8.4 Hz, 2H), 7.32 (d, J=7.80 Hz, 2H), 5.74–5.55 (m, 2H), 3.99 (d, J=5.60 Hz, 2H), 3.47–3.38 (m, 2H), 3.22–3.12 (m, 2H), 2.83 (t, J=7.00 Hz, 2H), 2.43 (s, 3H), 2.34–2.25 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 200.2 (CH), 143.6 (C), 136.0 (C), 131.2 (CH), 129.8 (CH), 128.6 (CH), 127.1 (CH), 48.4 (CH_2), 44.7 (CH_2), 43.9 (CH_2), 41.8 (CH_2), 31.4 (CH_2), 21.4 (CH_3). HRMS (ESI) calcd for $C_{15}H_{21}BrNO_3S^+$ $[M+H]^+$: 374.0420, found: 374.0415.

*3.5.4. 6-Exo-heterocyclization of 40: trans-1-tosyl-4-vinylpiperidine-3-carbaldehyde **42**.* $Pd(PPh_3)_4$ (9.5 mg; 8 μmol) was added to a solution of compound **40** (40.1 mg; 0.107 mmol) in THF (1.1 mL), followed by the addition of pyrrolidine (5.6 μL; 67 μmol) and triethylamine (15.3 μL; 0.110 mmol), and the reaction mixture was stirred at rt, under an argon atmosphere. After 1 h SiO_2 (150 mg) was added, the solvent was removed under reduced pressure, and the resulting slurry was submitted to column chromatography (SiO_2; petroleum–ether/EtOAc=45/10) to afford 25.9 mg (85%) of compound **42** as a colorless oil. The product was obtained as a mixture of stereoisomers in a ratio *trans*/*cis*=7.1/1.0. TLC R_f 0.53 (petroleum–ether/EtOAc=2/1). IR_{ATR}: 2923, 2850, 1721, 1641, 1596, 1340, 1162, 548. ^1H NMR for **42**-*trans* (500 MHz, $CDCl_3$) δ: 9.71 (d, J=1.5 Hz, 1H), 7.65 (d, J=8.5 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H), 5.76 (ddd, J^1=17.5 Hz, J^2=10.5 Hz, J^3=8.0 Hz, 1H), 5.13–5.06 (m, 2H), 3.86 (ddd, J^1=12.0 Hz, J^2=4.0 Hz, J^3=1.5 Hz, 1H), 3.72 (dtd, J^1=11.5 Hz, J^2=4.0 Hz, J^3=2.0 Hz, 1H), 2.57 (td, J^1=10.5 Hz, J^2=1.0 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, J^1=12.0 Hz, J^2=11.0 Hz, 1H), 2.33 (td, J^1=11.5 Hz, J^2=3.0 Hz, 1H), 2.22–2.16 (m, 1H), 1.80 (dq, J^1=13.5 Hz, J^2=3.5 Hz, 1H), 1.66 (dtd, J^1=13.5 Hz, J^2=11.2 Hz, J^3=4.2 Hz, 1H). ^{13}C NMR for **42**-*trans* (50 MHz, $CDCl_3$) δ: 202.3 (CH), 143.8 (C), 138.3 (CH), 132.7 (C), 129.8 (CH), 127.7 (CH), 117.1 (CH_2), 51.5 (CH), 45.3 (CH_2), 45.0 (CH_2), 40.8 (CH), 30.8 (CH_2), 21.5 (CH_3). HRMS (ESI) calcd for $C_{15}H_{20}NO_3S^+$ $[M+H]^+$: 294.1158, found: 294.1166; calcd for $C_{15}H_{19}NO_3SNa^+$ $[M+Na]^+$: 316.0978, found: 316.0975; calcd for $C_{15}H_{19}NO_3SK^+$ $[M+K]^+$: 332.0717, found: 332.0722.

*3.5.5. Catalytic asymmetric 5-exo-cyclization of 46: trans-diethyl 3-formyl-4-vinylcyclopentane-1,1-dicarboxylate **26**.* (*R*)-Ph-MeOBIPHEP (9.6 mg; 16.58 μmol) was added to a solution of palladium acetate (1.86 mg; 8.29 μmol) in THF (1 mL) and the resulting solution was stirred for 15 min at rt. The mixture was cooled to 0 °C, compound **46** (50 mg; 0.1185 mmol) was added and stirring was continued at that temperature. After 10 min, methyl cyclohexylamine (66.7 mg; 0.59 mmol) was added and stirring was continued for 2 h at 0 °C, followed by 20 h at 7 °C, when TLC (silica plates; eluent: toluene/ethanol=9/1 and petroleum–ether/EtOAc=9/1) indicated the complete consumption of the starting material. Silica (150 mg) was added, the reaction mixture was evaporated under reduced pressure and purified by column flash chromatography (2.5 g SiO_2; eluent: petroleum–ether/EtOAc=9/1) to give 24.1 mg (76%) of **26** as a colorless oil. The product was obtained as a mixture of diastereoisomers in a ratio *trans:cis*=7.4 : 1 (as determined by GC, and confirmed by integration of the corresponding peaks in ^1H NMR spectrum; see Supporting Information for details and copies of spectra). The optical purity of **26**-*trans* was >98% ee, and of **26**-cis was >98% ee (as determined by GC analysis on a chiral column; see Supplementary data for details and copies of chromatograms).

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Supplementary data

The supplementary data associated with this article can be found in the on-line version at, doi:10.1016/j.tet.2009.10.006.

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